

Pyoderma gangrenosum arising at the site of BCG immunization in a nine-month-old girl

Yuka Okura^a, Yasuyoshi Hiramatsu^a, Masaki Shimomura^a, Kota Taniguchi^a, Mitsuru Nawate^a, Yutaka Takahashi^a, Masahiro Ueki^b, Shunichiro Takezaki^b and Ichiro Kobayashi^a

^aDepartment of Pediatrics, KKR Sapporo Medical Center, Sapporo, Japan; ^bDepartment of Pediatrics, Hokkaido University Hospital, Sapporo, Japan

ABSTRACT

Pyoderma gangrenosum (PG) is an extremely rare disorder in children. We report a nine-month-old girl with PG who presented with high-grade fever and rapidly progressive ulcers at the site of a Bacillus Calmette-Guérin (BCG) inoculation 2 months after the immunization. Additional small pustules developed on her hand and posterior neck three months after the immunization and rapidly progressed. Cytokine profiling demonstrated elevated serum levels of interleukin (IL)-1 β , IL-10, IL-17A, IL-6 and IL-18, which is similar to adult cases. Genetic analysis identified heterozygous R202Q variant of the *MEFV* gene. All of her systemic and local symptoms responded to intravenous methylprednisolone pulse therapy followed by prednisolone 2mg/kg/day. There is no relapse of PG, to date, even after discontinuation of prednisolone. Atypical skin reactions after a BCG immunization could be an initial manifestation of infantile PG and need attention. Similarity of cytokine profile suggests common pathophysiology of infantile and adult PG.

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1. Introduction

Pyoderma gangrenosum (PG) is one of the neutrophilic dermatoses characterized by nodules or pustules progressing to a painful and rapidly expanding undermined ulcer with raised violaceous borders [1,2]. PG is a rare disorder with an estimated incidence of 3–10 cases per million people per year, with a peak between the ages of 20 and 60 years [1]. Pediatric PG patients aged <15 years account for only 4% of all PG cases [1,2], and infantile cases are further rare [3–27]. PG is considered as an autoinflammatory diseases, the pathophysiology remains poorly understood. Although cytokine profile and genetic background have been reported in adult PG [1], to date, studies on cytokines or genetics have not been reported in infantile PG except for monogenic PG such as pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. PG develops either spontaneously or following trauma, invasive procedure or vaccination. We, herein, report a nine-month-old girl with PG which arose at a Bacillus Calmette-Guérin (BCG) inoculation site who was successfully treated with systemic glucocorticoid alone.

2. Case presentation

A nine-month-old girl was referred to our hospital because of high-grade fever and rapidly progressive ulcers at the site of a BCG inoculation on her left upper arm. She was born to non-consanguineous healthy parents and had no medical history. There was no family history of hereditary autoinflammatory diseases. She had received a BCG immunization at the month of six. Red spots with small amounts of pus appeared at the needle marks one month after a BCG immunization, suggesting normal reaction. However, the redness of the site worsened two months after the BCG immunization. Three months after the immunization, blackish ulcers with new pustules appeared on the dorsum of the left hand and on the posterior neck. Because her ulcerative lesions and pustules rapidly progressed in two days accompanied by high-grade fever, she was referred to our hospital. On admission, she had undermined ulcers with raised erythematous borders on her left arm and two crusted nodules on her left hand and posterior neck (Figure 1(A–C)), with fever up to 39.6°C. Laboratory findings were as follows: white blood cell count $33.1 \times 10^9/L$ with 47.5% neutrophils,

CONTACT Ichiro Kobayashi  ichikoba@kk-smc.com  Center for Pediatric Allergy and Rheumatology, KKR Sapporo Medical Center, 3-40, Hiragishi 1-6, Toyohira-ku, Sapporo 062-0931, Japan

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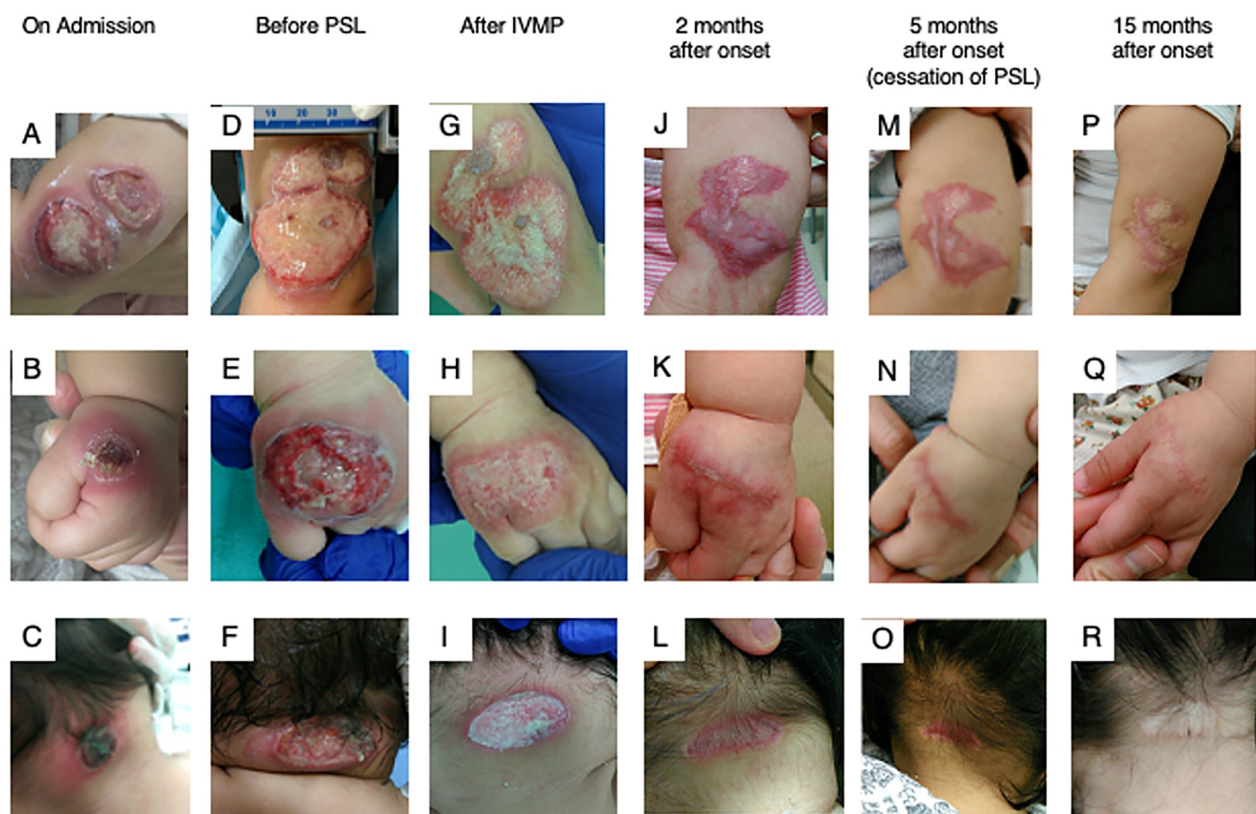


Figure 1. Chronological changes of skin lesions. Upper panel: the site of a BCG immunization on her left upper arm; middle panel: the lesion on her left hand; lower panel: the lesion on her posterior neck; PSL: prednisolone; IVMP: intravenous methylprednisolone.

hemoglobin 108g/L, platelet count $465 \times 10^9/L$, C-reactive protein (CRP) 57.6mg/L, immunoglobulin G 7.4g/L, C3 173mg/dL (normal range 80–140mg/dL), C4 40.5mg/dL (normal range 11.0–34.0mg/dL), CH50 89.5U/mL (normal range 30–45U/mL), ferritin 103.3ng/mL (normal range 5.0–157.0mg/mL), and soluble IL-2 receptor 1167U/mL (normal range 122–496U/mL). Her fever and skin lesions failed to respond to an initial empiric intravenous antibiotic therapy. Skin biopsy from the margin of the lesion around the BCG site showed a dense neutrophil-rich infiltrate that spanned the dermis and extended into the subcutis without vasculitis (Figure 2(A,B)). No pathogenic organisms were cultured from blood or skin pustules. As well, mycobacterial genome was not detected from biopsied samples by polymerase chain reaction. During a few days, ulceration with peripheral erythema of her hand and neck and ulcerative lesions on her left arm progressed in both size and depth (Figure 1(D–F)). New several pustules developed at the site of catheterization suggesting pathergy phenomenon. She was diagnosed as having PG based on clinical manifestations, negative bacterial culture and histopathological findings. Prednisolone 1mg/kg/day was commenced for progressive skin ulceration, new pustules and persisted high-grade fever, resulting in partial resolution of her fever. Intravenous methylprednisolone pulse (IVMP) therapy (30mg/kg/day for

3 consecutive days) followed by prednisolone 18mg/day (2mg/kg) for 2 weeks achieved complete resolution of fever and skin lesions (Figure 1(G–I)). The dose of prednisolone was decreased to 15mg/day, 12mg and 10mg, and then by 1mg every 1–2 weeks. Prednisolone was finally discontinued after 5 months of treatment. The skin lesions gradually recovered without relapse (Figure 1(J–R)). She is now 24-month-old and good in health with no obvious systemic complication.

We measured levels of interleukin (IL)-1 β , interferon (IFN)- α 2, IFN- γ , tumor necrosis factor- α , IL-10, IL-12p70, IL-17A, IL-23, IL-6, IL-33, monocyte chemoattractant protein (MCP)1, IL-8 and IL-18 by LEGENDplex Human Inflammation Panel 1 (BioLegend, San Diego, CA) in the sera obtained at her admission and 3 weeks after IVMP therapy. Control sera were obtained from 4 age-matched healthy individuals. The levels of IL-1 β , IL-10, IL-17A, IL-6 and IL-18 were higher than normal control before the treatment with IVMP and declined to healthy control or near-normal levels three weeks after IVMP (Figure 3). Genetic analyses by gene panel screening of autoinflammatory diseases identified heterozygous R202Q variant of the *MEFV* gene but no variant of the other autoinflammation-related genes such as *PTSPI1*, *ADA2*, *NLRC4*, *TNFAIP3*, *TNFRSF1A*, *NLRP3*, *NLRP12*, *MVK*, *PLCG2* and *NOD2*.

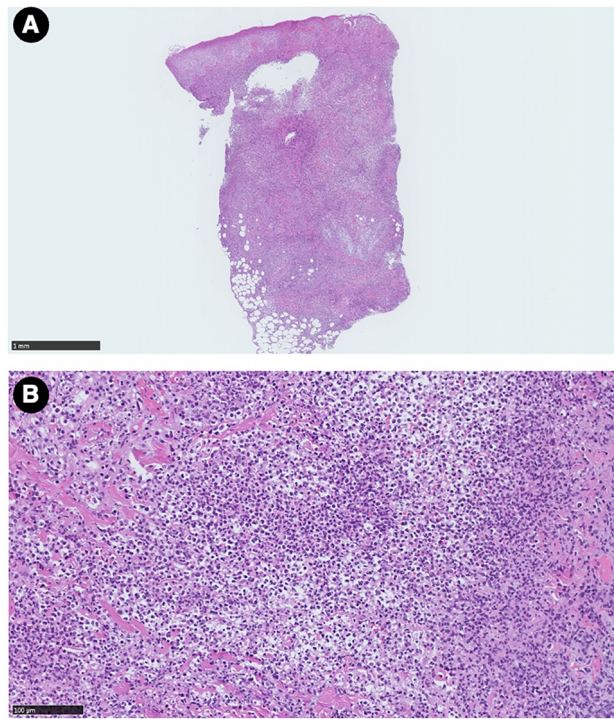


Figure 2. Skin biopsy. Dense cellular infiltration extends from epidermis to subcutaneous panniculus (A, H-E staining). Infiltration of predominantly neutrophils is evident in the dermis (B, H-E staining). No caseous necrosis or granuloma was detected.

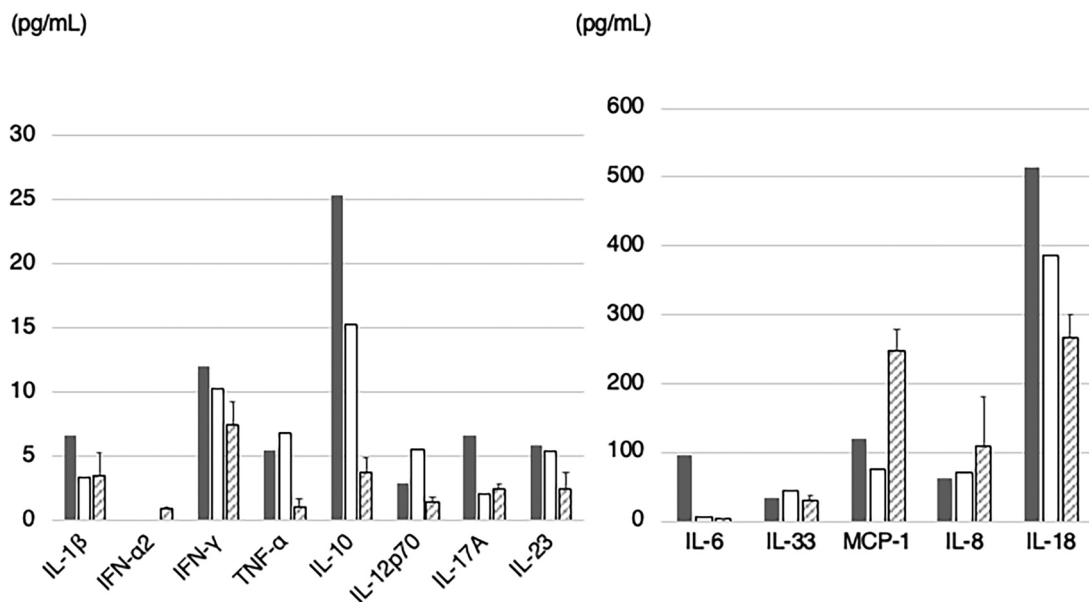


Figure 3. Serum levels of cytokines and chemokines. The figure shows serum levels of interleukin (IL)-1 β , interferon (IFN)- α 2, IFN- γ , tumor necrosis factor- α , IL-10, IL-12p70, IL-17A, IL-23, IL-6, IL-33, monocyte chemoattractant protein (MCP)1, IL-8 and IL-18 in our patient before (closed bar) and after (hatched bar) IVMP therapy and age-matched healthy control (open bar). IVMP: intravenous methylprednisolone.

3. Discussion

We report a nine-month-old girl with PG which initially arose at the site of a BCG inoculation and expanded to other sites. To date, 26 cases of infantile PG have been reported (Table 1) [3–27]. Table 2 summarizes clinical and laboratory features of the 27 patients including our patient. Mean age of onset was 8.5 months old (IQR: 6–9), although neonatal onset

was described in two cases. There was no sex difference (M:F = 14:13). Twenty-four cases presented with multiple lesions, whereas only three cases showed single lesion. Fever (71.4%), multiple lesions (88.9%), leukocytosis (85.7%) and elevated CRP levels (100%) are commonly observed. In our patient, new pustules developed at the site of venipuncture indicating pathergy. Pathergy is observed in one-third of patients with PG [1,2].

Table 1. Clinical features and treatment of reported infantile pyoderma gangrenosum.

Study	Year	Age of onset/sex	Lesion	Fever	WBC (/μL)	CRP (mg/dL)	Systemic GC	Other systemic drugs	Topical ointment	Comorbidity
Dick et al. [3]	1982	9 Mo/F	Multiple	Yes	41,900	N/A	Oral GC		None	
Paller et al. [4]	1990	9 Mo/F	Multiple	Yes	N/A	N/A	None		GC	HIV
Glass et al. [5]	1991	7 Mo/M	Multiple	Yes	21,900	N/A	Oral GC	DDS	GC	TA, died
Sood et al. [6]	1992	6 Mo/M	Multiple	Yes	14,500	N/A	IV GC	DDS	None	
Graham et al. [7]	1994	2 D/M	Multiple	No	Normal	N/A	None		GC	
Dagan et al. [8]	1995	9 Mo/M	Multiple	Yes	18,300	4+	Oral GS	DDS, COLC, AZP	None	CRMO, TA
Khatri et al. [9]	1995	8 Mo/M	Multiple	Yes	39,000	N/A	Oral GC	DDS	None	
		9 Mo/F	Multiple	N/A	N/A	N/A	None	DDS	None	
Merke et al. [10]	1996	9 Mo/M	Multiple	Yes	64,300	N/A	IV and oral GC	DDS	None	
Al-Rimawi et al. [11]	1996	9 Mo/F	Multiple	N/A	Normal	N/A	Oral GC		None	
Gümruk et al. [12]	2000	11 Mo/F	Multiple	N/A	66,000	N/A	Oral GC		None	MDS
Ravi and Sanju [13]	2000	10 Mo/M	Multiple	N/A	N/A	N/A	Oral GC		None	
Lesmeister et al. [14]	2002	8 Mo/M	Multiple	Yes	Leukocytosis	10	None	IVIG, ANK, IFX	None	
Koturoglu et al. [15]	2006	6 Mo/M	Multiple	Yes	19,000	6.6	Oral GC		GC	CRMO
Torrel et al. [16]	2006	6 Mo/F	Multiple	Yes	33,140	N/A	Oral GC		Tac	
Mehta and Charman [17]	2006	10 Mo/F	Single	No	Normal	N/A	None		GC	AIN
Dinulos et al. [18]	2006	9 Mo/F	Multiple	N/A	24,000	11.2	IV and oral GC	SASP, MP	None	CD
McAleer et al. [19]	2008	8 Mo/M	Multiple	N/A	N/A	1.08	Oral GC	CsA	GC	
Rajan et al. [20]	2008	3 Mo/F	Multiple	No	17,600	13.7	IVMP	DDS, CsA, IFX	GC	
Sarma et al. [21]	2012	4 Mo/F	Multiple	Yes	22,600	N/A	Oral GC		None	
Carneiro et al. [22]	2013	13 D/M	Multiple	N/A	N/A	N/A	Oral GC		None	
Campos-Muñoz et al. [23]	2014	11 Mo/M	Multiple	Yes	21,200	N/A	Oral GC	DDS, CsA, IFX	None	
Etzler et al. [24]	2015	10 Mo/F	Single	Yes	High	High	GC	COLC, CsA, IFX, ANK	None	
Crouse et al. [25]	2018	9 Mo/F	Multiple	Yes	N/A	N/A	Oral GC, IVMP	IFX, Tac	Tac, DDS	
Mansh et al. [26]	2018	8 Mo/M	Multiple	No	22,000	N/A	IV GC	ANK	GC	
Diez et al. [27]	2020	1 Mo/M	Single	No	Leukocytosis	29.0	IV GC	IVIG, ANK, IFX	None	
Present study	2023	9 Mo/F	Multiple	Yes	33,100	5.76	IV GC, IVMP oral GC	None	GC	

AIN: autoimmune neutropenia; ANK: anakinra; AZP: azathioprine; CD: Crohn's disease; COLC: colchicine; CRMO: chronic recurrent multifocal osteomyelitis; CRP: C-reactive protein; CsA: cyclosporine A; D: days old; DDS: diaphenylsulfone; F: female; GC: glucocorticoid; HIV: human immunodeficiency virus; IFX: infliximab; IVIG: intravenous immunoglobulin; IVMP: intravenous methylprednisolone; M: male; MDS: myelodysplastic syndrome; Mo: months old; N/A: not available; SASP: sulfasalazopyridine; TA: Takayasu's arteritis; Tac: tacrolimus; WBC: white blood count.

Our patient was, to date, not complicated by other systemic inflammatory disease. Underlying systemic immune-mediated disorder complicates in a half of adult PG patients but in only seven patients (27%) with infantile PG [4,5,8,12,15,17,18]. Although underlying diseases mostly precede the onset of PG, one case developed Takayasu's arteritis 3 years after the onset of PG onset [8]. Thus, long-term observation is necessary in cases without underlying diseases.

Our patient showed chronic eruption at the inoculation site which deteriorated 2 months after BCG immunization. Two cases of infantile PG following vaccination have been reported; PG developed several days after a diphtheria–pertussis–tetanus vaccination in a 7-month-old boy and 1 week after measles vaccination in a 9-month-old girl [5,9]. This is contrast to our patient with long asymptomatic period. BCG is a long-living bacteria and inoculated

intradermally, whereas the other vaccines are intramuscularly or subcutaneously inoculated inactivated bacteria, bacterial components or live-attenuated viruses. Thus, the difference in the nature or inoculation site of the vaccination may attribute to different reaction.

Our patient showed elevated serum levels of IL-1 β , IL-6, IL-17A and IL-18, which is consistent with adult cases [28–30]. IL-17 recruits neutrophils directly or mediated by induction of IL-8 which is a potent chemokine and elevated in adult PG [28–32]. Lack of elevated IL-8 in our patient may reflect expression of IL-8 limited to the localized lesions.

The cytokine profile in our patient raises the possibility of involvement of inflammasome and IL-6-induced differentiation of Th17 cells [32]. Genetic analysis demonstrated heterozygous R202Q variant of the *MEFV* gene in our patient. Pyrin, encoded by

Table 2. Summary of characteristics of infantile pyoderma gangrenosum.

Characteristics	n = 27 ^a
Boy (%)	14 (51.9%)
Age at onset	
Months (average)	7.3
Range	Day 2–11 months
Lesion	
Multiple	24 (88.9%)
Systemic symptoms	
Fever	15/21 (71.4%)
Leukocytosis	18/21 (85.7%)
Elevated CRP	9/9 (100%)
Treatment	
Systemic GC only	9 (33.3%)
Systemic GC plus other systemic drugs	13 (48.1%)
Systemic drugs except for GC	2 (7.4%)
No systemic drugs	3 (11.1%)
Comorbidities	7 (25.9%)
Takayasu's arteritis	1
Takayasu's arteritis, sterile multifocal osteomyelitis	1
Sterile multifocal osteomyelitis	1
Crohn's disease	1
Autoimmune neutropenia	1
Human immunodeficiency virus infection	1
Myelodysplastic syndrome	1

^aIncluding our patient.

the *MEFV* gene, is a key component of pyrin inflammasome and mediates activation of IL-1 β and IL-18. In addition to familial Mediterranean fever (FMF), mutations in the *MEFV* gene cause pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) [33]. Heterozygous R202Q of the *MEFV* gene is detected in six of 13 (46%) non-syndromic PG patients [34] and neutrophilic dermatosis [35,36]. On the other hand, functional abnormality of the variant is not detected at least in experimental conditions [33,37]. Furthermore, this variant is observed in 3–4% of Japanese [38] and up to 36% of Caucasian populations (https://infervers.umai-montpellier.fr/web/detail_mutation.php). Thus, R202Q of *MEFV* could be a candidate for a susceptibility variant of PG but unlikely a pathogenic mutation.

Both fever and skin lesions were well controlled by the treatments with IVMP and subsequent prednisolone in our patient. Systemic glucocorticoid is used in 22 patients (81.5%) with infantile PG and a mainstay of the treatment, although 13 cases required additional medication such as dapsone, infliximab, cyclosporine A, anakinra, colchicine, intravenous immunoglobulin, tacrolimus and azathioprine (Table 2). Concomitant immunosuppressive therapy should be considered in glucocorticoid-dependent or refractory cases following the strategy for adult PG [39].

Conclusively, we report a nine-month-old girl with PG which arose at the site of a BCG immunization. Atypical skin reactions after a BCG immunization could be an initial manifestation of infantile PG. Cytokine profile suggest a pathophysiological role of inflammasome in the development of PG in both infants and adults. R202Q variant of the *MEFV*

may contribute to susceptibility of PG. More than three-fourth of infantile PG is isolated case and needs early diagnosis and intervention with systemic glucocorticoid therapy.

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Consent form

Written informed consent to publish this case report was obtained from the patient's guardians.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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